STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: Esomeprazole
ACTIVE INGREDIENT: Esomeprazole

Study No: D9612L00111
Evaluation of the efficacy of three strategies of long-term management of symptoms of gastroesophageal reflux in general medicine: a multicentre, randomised, open label study conducted in parallel groups

Developmental phase: Phase IV
Study Completion Date: LSLV = 25 August 2008
Date of Report: 10 August 2009

Synopsis of Clinical Study Report

Study product: Esomeprazole

Study code: D9612L00111

Edition number: 3

Date: 10 August 2009

Evaluation of the efficacy of three strategies of long-term management of symptoms of gastroesophageal reflux in general medicine: a multicentre, randomised, open label study conducted in parallel groups

Date of study: First patient in: 1 March 2007

Last patient - last visit : 25 August 2008

Last patient out: 7 October 2008

Phase of development: Therapeutic use (IV)

This study has been conducted according to good clinical practices, including archiving of study documents.

Investigating centre(s)

The study was conducted by 865 General Practitioners acting as investigators in France.

Publications

None at the time of writing of this report

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and variables in the study

Objectives	Variables in the study	type
Primary	**Primary**	
To compare the efficacy of three strategies of long-term treatment	Number of failures of treatment during the maintenance treatment phase	Efficacy
Secondary	**Secondary**	
To evaluate whether the RDQ (Reflux Disease Questionnaire) provides additional information to the clinical assessment by the investigator at the time of initial evaluation of symptoms, and facilitates the decision of choice of treatment	RDQ questionnaire score Strategy of treatment chosen by the investigator at the time of visit one for the initial treatment phase and planned strategy for the maintenance treatment phase Clinical judgment of the investigator on the severity of symptoms of GOR (mild, moderate, severe)	Efficacy
To evaluate the impact of treatment with low dose aspirin (ASA) used concomitantly during the initial phase and the maintenance phase	Type and dose of aspirin used during the initial phase, the maintenance phase and during the entire study	Efficacy
To evaluate the differences among strategies of maintenance treatment for satisfaction of the patient, using the GIS scale (GORD Impact Scale).	Scores derived from the GIS questionnaire at the start and at the end of the maintenance phase.	Efficacy
To evaluate the impact of anxiety and depression during the initial visit measured by the HADS (Hospital anxiety and Depression scale) questionnaire on response to initial treatment and to maintenance treatment	Response to initial treatment and maintenance treatment based on responses to the HADS questionnaire	Efficacy
To describe the number and type of serious adverse events and adverse events leading to a premature discontinuation of the study	Number and type of serious adverse events and adverse events leading to premature discontinuation of the study	Safety
To create score abacuses based on the RDQ questionnaire, which may be used to evaluate the severity of symptoms during the initial visit.	RDQ score and severity of symptoms evaluated by the investigator	Exploratory *
To create score abacuses based on the RDQ questionnaire, which may be used to offer patients a strategy of treatment during the initial phase and in the long term	RDQ score and clinical judgment of the investigator, taking into account the severity of symptoms of reflux (mild, moderate and severe)	Exploratory *
To create score abacuses based on the RDQ questionnaire which may be used to define the success of treatment	RDQ score and number of treatment failures during the maintenance treatment phase	Exploratory *

* the results of exploratory analyses were not available at the time of writing of the clinical study report

Design of the study
This is a multicentre, randomised, open-label study conducted on parallel groups in patients presenting with symptoms attributed to GER according to the evaluation of the general practitioner at the time of enrolment.

The study included two phases for a maximum duration of treatment of 16 weeks: one initial treatment phase of 4 weeks, from visit 1 to visit 2, and one randomised maintenance treatment phase of 12 weeks (only for patients whose treatment is considered to be successful at the end of the initial phase), from visit 2 to visit 3.

During the initial phase, the patients received, once daily, either esomeprazole 20 mg or esomeprazole 40 mg, depending on the decision of the investigator at visit 1.

During the maintenance treatment phase, patients were randomized to one of the following three groups: group 1: esomeprazole 20 mg once daily, group 2 : esomeprazole 20 mg on demand (with a maximum dose of one tablet per 24 hours) and group 3 : antacid treatment as needed (Xolaam® maximum six tablets per day).

Target population and size of the sample

The target population was comprised of patients of both sexes, 18-50 years of age consulting a general practitioner for symptoms attributed to gastroesophageal reflux. Patients had to be eligible, according to the judgment of the investigator, for empirical treatment of at least 16 weeks, with esomeprazole or another antacid. Patients having received treatment with PPI or anti-H2 for diagnosis of GER within the three months prior to the initial visit could not be included in the study.

Approximately 6000 patients were to be enrolled in the initial treatment phase in order to randomise approximately 5100 patients in the maintenance treatment phase. The expected proportions of patients with treatment failure at the end of the maintenance treatment phase were: 10% in group 1, 20% in group 2 and 60% in group 3, regardless of the severity of the symptoms at baseline. This setup should have led to a power of 85% with an alpha significance level of 0.017 (level of significance of the third test of the Bonferroni-Holm procedure).

Planned number of patients was not reached at the end of the recruitment period. Statistical analysis plan was revised accordingly prior cleanfile, with the assumption of 3300 patients enrolled. Comparisons between treatment arms were performed globally and with adjustment according to severity. No stratified analysis was undertaken.

Treatment studied and reference treatments: dosage, method of administration and batch numbers

Study product or other treatment	Form, dosage, dose, method of administration	Manufacturer	Formulation number	Batch numbers (expiration date)
INEXIUM®	Tablets, 20 mg, oral route	AstraZeneca Monts (France) AstraZeneca AB Södertälje (Sweden)	Not available	HK 16698 (10/2008) HK16647 (09/2008)
XOLAAM®	Tablets, total antacid capacity: 14.71 mmol of H+ ions, oral route	Sanofi Aventis Origgio (Italy)	Not available	258 (10/2011)

Duration of treatment

Initial treatment phase (four weeks): During this phase, patients received, once daily, esomeprazole 20 mg or 40 mg depending on the decision of the investigator at visit 1.

Maintenance treatment phase (12 weeks): depending on randomisation, the patients followed one of the following three treatments: esomeprazole 20 mg once daily; esomeprazole 20 mg on demand; antacid treatment (Xolaam®) as needed.

Statistical methods

Analysis of the primary endpoint was performed on the ITTe population based on treatment strategy groups in the maintenance phase for the primary analysis. Treatment failure was defined based on responses to the following two questions (if at least one negative response was given, the patient was considered to be in failure of maintenance treatment):

- Did the treatment produce sufficient control of your reflux symptoms?
- Do you wish to continue this treatment?

In order to compare the efficacy of the three treatment strategies, the number and percentage of treatment failures were calculated separately for each group. Comparisons were made on the total population using a two-sided Fisher test leading to three comparisons between groups: group 1 versus group 2, group 2 versus group 3, group 1 versus group 3. Adjustment for multiple comparisons was performed according to the sequential Holm-Bonferroni method (k = 3 tests), in order to control the level of significance (alpha = 0.05) of these 3 tests.

For the other criteria, the descriptions were performed by randomization group and overall.

Target population

The populations for analysis are as follows:

- ***Safety population of the initial treatment phase (PTi):***

This population is made up of all patients included at visit 1 who took at least one dose of treatment during the 4 weeks of the initial treatment phase and for whom information after the administration of treatment is available.

- ***Intention to Treat population of the initial treatment phase (ITTi):***

This population is made up of all patients in the safety population who have an assessable RDQ questionnaire (less than 50% of missing data) for visits 1 and 2 and for whom information on the severity of symptoms at time of inclusion is available.

- ***Safety population of the maintenance treatment phase (PTe):***

This population is made up of all patients randomized at visit 2 who took at least one dose of treatment during the 12 weeks of the maintenance treatment phase and for whom information after the administration of treatment is available.

Intention to Treat population of the maintenance treatment phase (ITTe):

This population is made up of all patients of the maintenance phase safety population for whom a treatment failure determination is possible based on the information contained in the case report form.

In all, 3140 patients were selected .

The number of patients in each population to be analyzed is as follows:

- PTi population: 3032 patients,
- ITTi population: 2689 patients,
- Randomised population: 2685 patients,
- PTe population: 2617 patients,
- ITTe population: 2558 patients.

The mean age of the patients at inclusion was 41 years in the ITTi population (initial phase population to be analyzed). 62% of the patients presented with a history of reflux symptoms. Median time since onset of these symptoms was 2 years (min; max=0; 41). Of the patients treated with esomeprazole 20 mg, 22% presented with mild symptoms, 73% with moderate symptoms and 6% with severe symptoms. Of the patients treated with esomeprazole 40 mg, 4% presented with mild symptoms, 55% with moderate symptoms and 41% with severe symptoms.

At the end of the initial phase, a successful treatment outcome was considered to be any patient who reported retrosternal burning or distressing regurgitation of the stomach contents on fewer than 2 days out of the last 7 days and whose symptom intensity score was "not at all", "very slight" or "slight". Initial treatment was considered to be successful in 85% of cases.

At randomization, ie initiation of the maintenance phase, the 3 treatment strategy groups were well balanced in terms of clinical characteristics.

Summary of results regarding efficacy

Analysis of efficacy showed that:
In the ITTe population at visit 3, 11% of patients of the esomeprazole 20 mg continuous group, 8% of patients in the esomeprazole 20 mg on demand group and 43% of patients in the antacid group were in failure of maintenance treatment. Statistical analysis showed a clinically meaningful significant difference in favour of esomeprazole regardless of the dosage regimen used (continuous or on demand) as compared to antacid treatment ($p<0.0001$).

Between the two esomeprazole groups, a marginal statistical significant difference was observed in favor of esomeprazole on demand as compared to continuous esomeprazole ($p= 0.0484$), which was not confirmed in the sensitivity analysis ($p=0.2171$) including the patients for whom the assessment of primary criteria was not available and therefore, analyzed as treatment failure.

All patients included in the study had to complete a RDQ questionnaire on reflux. After reading this questionnaire:

- The physician investigator would have evaluated the severity of symptoms differently as compared to his clinical judgment in 8% of cases.
- As compared to his initial assumption, the investigator would have assigned the other initial phase treatment to 3% of patients and a different maintenance treatment strategy to 5% of patients.

The patients also had to complete a GIS questionnaire (GORD Impact Scale) at each visit. Overall, the GIS scores showed minimal variation during the maintenance phase, irrespective of the treatment allocated by the randomization procedure.

According to HADS questionnaire (Hospital Anxiety and Depression Scale), depression had no impact on initial treatment success. With regard to anxiety : treatment success was observed in 89%, 85% and 76% of patients without, with possible and with anxiety respectively.
No impact of depression and anxiety was noted during maintenance phase.

Summary of results regarding safety
Only serious adverse events and adverse events leading to study treatment discontinuation were to be reported in the study.

A total of 19 patients had 19 serious adverse events during the study: 10 serious adverse events occurred during the initial phase and 9 during the maintenance phase.
Among these 19 patients, 2 deaths, not treatment related, were reported (lung cancer).

A total of 74 adverse events involving discontinuation of treatment (serious and non serious taken together) occurred during the study (55 patients in all, i.e. 37 patients and 18 patients for each phase, respectively): 54 events during the initial phase and 20 events during the maintenance phase.
Overall, treatments were well tolerated.